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Do You Get What You Paid For? An Examination of Products Advertised as Kratom

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ABSTRACT
Although some novel psychoactive substances (NPS) are newly discovered chemicals, others are traditional or indigenous substances that are introduced to new markets. One of these latter substances is a plant many people refer to as kratom. Indigenous to Southeast Asia and used for a variety of instrumental and recreational purposes, kratom has recently become available to Western drug users. Kratom is somewhat unique in that the plant contains two different psychoactive chemicals, which have both stimulant (mitragynine) and narcotic (7-hydroxymitragynine) properties. Thus, kratom may appeal to different types of drug users for reasons other than curiosity. In the current study, 15 samples of products that were either directly advertised as kratom or were listed in the results of a web search (but were not directly advertised as kratom) were purchased for testing. After laboratory testing, it was determined that all products advertised as kratom contained the active chemical mitragynine, but 7-hydroxymitragynine was not detected in any of the samples. Implications are discussed.

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Prohibitionist drug policies create black markets that offer unregulated drugs with unknown safety and purity (Thornton 1998). This is especially problematic with drugs such as heroin, with which even an experienced user can accidentally overdose (Desmond, Maddux, and Trevino 1978). Additionally, these drugs are often mislabeled by black market sellers and/or contain impurities and adulterants. While a common issue for many drugs, it is especially prevalent with MDMA (Parrott 2004). In addition to substances that are already documented and controlled, users may turn to novel psychoactive substances (NPS) in an effort to obtain substances that will produce the same pharmacological effects as illegal drugs, but not carry the same criminal penalties. Yet, at times, NPS that are specifically advertised as "legal highs" may contain either prohibited and/or regulated substances (Winstock and Ramsey 2010). One of the main attractions of NPS is that these substances can be purchased from legitimate markets, either through the Internet or in head shops, quite different from the manner in which illegal drugs are often procured (Schmidt et al. 2011). While it may be safer procuring legal substances, there is still concern about whether these substances are, in effect, as advertised (Baron, Elie, and Elie 2011). One of these emerging substances with very few legal restrictions is a substance commonly referred to as kratom.

Kratom

In 1836, the first scientific reference was made to *Mitragynine speciosa* (kratom), a tree native to Africa and Southeast Asia, primarily found in Thailand and Malaysia. The leaves of the plant contain over 20 alkaloids, with multiple alkaloids producing psychoactive properties (Jansen and Prast 1988). Mitragynine ((*E*)-2-[(2*S*,3*S*)-3-ethyl-8-methoxy-1,2,3,4,6,7,12,12b- octahydroindolo[3,2-h]quinolizin-2-yl]-3- methoxyprop-2-enoic acid methyl ester) is the primary alkaloid in kratom. It is a partial opioid agonist that has one-fourth the potency of morphine. A minor alkaloid also found in the plant, 7-hydroxymitragynine (7-OH), is 10 times as potent as morphine (Babu, McCurdy, and Boyer 2008; Kitajima et al. 2006). Opioid antagonists are known to precipitate withdrawal (Kamei and Ohsawa 1997). While kratom use can produce dependency, kratom withdrawal symptoms appear to be more moderate than withdrawal symptoms from opiates (Boyer et al. 2008). Recent evidence has demonstrated that kratom is used regularly with only small impairments

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of social functioning, in contrast to opiates (Singh, Müller, and Vicknasingam 2014). Kratom can be ingested in many forms, including smoking or chewing the leaves; brewing the leaves into a tea; powdered leaves in capsule or pill form; or an extract can be made into a liquid dose. Additives, such as sugar or honey, are often added to kratom to marginalize the bitter natural taste of the substance (Hassan et al. 2013).

Historically, kratom was used as a treatment for malaria, cough, hypertension, diarrhea, depression, analgesia, fever reduction, and mediation of opioid withdrawal. Originally known to Westerners only as an opiate substitute, further testing of kratom confirmed that mitragynine was actually a central nervous stimulant. Initially, kratom was compared to cocaine (Jansen and Prast 1988). Thus, it seems that, in smaller doses, kratom acts as a stimulant, while in larger doses kratom acts as an opiate. Such dual effects within a substance are rare (Babu et al. 2008; Hassan et al. 2013; Jansen and Prast 1988; Kikura-Hanajiri et al. 2009; Rosenbaum, Carreiro, and Babu 2012; Scott, Yeakel, and Logan 2014). Animal studies have shown that there is a complex psychostimulant and opioid-like dose-response curve for several behavioral effects of kratom (Yusoff et al. 2016). However, the composition of kratom plants can vary with geography, and considerable variation has been found in the amounts of psychoactive compounds within different plants (Kowalczuk, Łozak, and Zjawiony 2013).

Within Southeast Asia, manual laborers have reported using kratom to increase energy levels so that they could work longer hours. At the same time, chronic use produced comparable effects to long-term users of opiates. Since kratom also functions as an opiate agonist, it has been recognized as a way to treat opiate abuse (Jansen and Prast 1988; Rosenbaum, Carreiro, and Babu 2012; Saingam et al. 2013; Swogger et al. 2015). Boyer et al. (2008), for example, documented a patient who had ceased injecting hydromorphone and substituted his opiate use with kratom. Although kratom is indigenous to Thailand and Malaysia, the substance is controlled in both countries. In 1979, Thailand placed kratom in Schedule 5 of the Thai Narcotics Act; in 2003, Malaysia listed kratom in the Poison Act (Hassan et al. 2013). Yet, as Ahmad and Aziz (2012) discovered, kratom is still commonly used in both countries. Using both convenience and snowball-sampling methods, they recruited 562 respondents, 88% of whom reported daily use of kratom. Among the rationales provided for using the drug were social and recreational needs, stamina and physical endurance, pain relief, and improved sexual performance. Other countries control or regulate kratom, including Bhutan, Finland, Lithuania, Denmark, Poland, Sweden, Australia, and Myanmar. In the United States, the Drug Enforcement Administration has only listed kratom as a drug of concern (Hassan et al. 2013). More recently, the Centers for Disease Control and Prevention (CDC) declared that kratom was "an emerging public health threat" (Anwar and Schier 2016). Kratom is controlled at the state level in Alabama (mitragynine and 7-OH), Tennessee, Indiana, Wisconsin, and Vermont. There is legislation pending to control kratom in Indiana, Michigan, and New Jersey. In Arizona, Oklahoma, Louisiana, Illinois, and Florida, initial attempts to control kratom failed.

Kratom is available for purchase on the Internet, in convenience stores, gas stations, and head shops (Kowalczuk, Łozak, and Zjawiony 2013; Rosenbaum, Carreiro, and Babu 2012). Some drug users may purchase kratom simply to produce pharmacological effects without fear of legal repercussions. However, kratom may have wide appeal among drug users because it produces stimulant-like effects, opiate-like effects, and can be used as a legal means to treat opiate withdrawal. Thus, kratom has the potential to be purchased and used for more than simple curiosity of polydrug users (Boyer et al. 2008; Cinosi et al. 2015; Kowalczuk, Łozak, and Zjawiony 2013; Rosenbaum, Carreiro, and Babu 2012). Additionally, many websites advertise that kratom can be used for the treatment of panic attacks.

Research has shown that kratom is sometimes sought by heroin users when they are unable to obtain any heroin (Ahmad and Aziz 2012; Singh, Müller, and Vicknasingam 2014; Vicknasingam et al. 2010). This leads to two questions: what are the dangers to kratom users, and do items advertised as kratom actually contain kratom? Kratom toxicity is poorly understood. However, there is some evidence that kratom use can cause seizure, coma, and even death (Boyer et al. 2008; Nelsen et al. 2010; Rosenbaum, Carreiro, and Babu 2012). Until recently, most reports have involved polydrug abuse. For instance, in 2011, fatalities were associated with a substance called Krypton, a mixture of kratom and O-Desmethyltradmadol (Kronstrand et al. 2011). More recently, in 2014, during the autopsy of a middle-aged Norwegian man, it was determined that he had mitragynine at 1.06 mg/L and 7-OH at 0.15 mg/L while Zopiclone, citalopram, and lamotrigine were present at therapeutic levels (Karinen et al. 2014). In a survey of regular kratom users in Malaysia, Singh, Müller, and Vicknasingam (2014) found that 45% of 293 regular users showed signs of moderate kratom dependence. Adulterants added to samples of kratom can bring both additive pharmacological effect and increased danger to users (Philipp et al. 2009). Additionally, there are lab testing procedures available to assess different varieties of kratom and these methods have been used by researchers on samples of kratom purchased from online sellers (Kowalczuk, Łozak, and Zjawiony 2013).

Kratom vendors advertise by potency, vein color, and geographical origin. Any claims of potency based on these criteria have not been substantiated. As Suwanlert (1975) reported, users in Thailand prefer white-vein kratom for its stronger effect, while Chittrakarn, Penjamras, and Keawpradub (2012) reported that red is preferred over the less potent green. Chemical analysis has linked potency to geographical source, but the season, age of sample, as well as the part and age of the plant can also affect potency. Botanists have also classified kratom by geographical source: Bali, Indonesia, Malaysian, Borneo, New Guinea, Java, Indonesian Island, Sumatra, and Riau (a province in Indonesia) (Eisenman 2014).

Materials and methods

The aim of the current study was to test a variety of products advertised as kratom from sources from which users are likely to purchase the drug. To identify kratom products available for purchase, the term "kratom" was entered into a search window. Most of the hits were for kratom powders or capsules. Fifteen samples of kratom were purchased. Eleven of these samples were purchased from a popular online retail store that includes products from a variety of different vendors. Two kratom samples were purchased from a local head shop and two samples of the same brand of liquid pain reliever with kratom listed as an ingredient on the label were purchased from a convenience store that one of the researchers commonly frequents.

Several of the search results mentioned pain relief or stress relief. Three such samples were purchased: pain relievers in liquid and pill form and a stress reliever in pill form. The two products in pill form did not list kratom or mitragynine on the label. All purchases were shipped from the continental United States. In total, nine of the samples were ground, dried plant material, either as a loose powder or a powder in capsule form; two samples were in pill form; and four samples were in liquid form.

Standards of mitragynine and 7-OH were purchased from Cerilliant Corporation. Chloroform, NaOH, and HCl were purchased from Fisher Chemical and used as received. The samples were run on an Agilent Technologies Gas Chromatography/Mass Spectrometer (GC-MS) with a 6890 N Network GC System and a 5975 Inert Mass Selection Detector. The instrument was equipped with a 7683B Series Injector and a 7683 Series Autosampler. The column was a DB-5 column (30 m x 0.25 nm, with 0.25 µm film thickness) with helium at a constant flow rate of 1.1 ml/min. The split ratio was 15:1 and the injection volume was 2.0 µl. The injection port temperature was set at 260°C. The oven temperature program was as follows: initial temperature of 150°C held for two minutes, then a ramp of 20°C/min to 275°C, with a final hold of 20 minutes for a total run time of 28.25 minutes. Dibucaine was selected as the internal standard and was prepared in chloroform at a final concentration of 0.1 mg/ml.

The powder samples were extracted as received. The pills were ground into a powder with a mortar and pestle. A total of 500 mg of the sample were transferred to a 25 ml Erlenmeyer flask of the sample and 15 ml of CHCl3 was added. The flask was placed in a sonicator for 30 minutes. After sonication, the sample was filtered into a beaker using Whatman Number 4 filter paper. The sample was placed on a hot plate and reduced to 2 ml. Fifty microliters of dibucaine were then added and the sample was analyzed by GC-MS.

The four liquid samples were prepared for analysis using an acid/basic extraction. Three ml of the sample was placed in a test tube and acidified with 10 drops of 0.1 M HCl to pH 1. Three ml of chloroform were then added and the solution was mixed. The chloroform layer was removed. The pH of the aqueous layer was raised to 10 with 4 M NaOH. Three ml of CHCl3 were added and the solution was mixed. The chloroform layer was removed, placed in a GC vial, and analyzed by GC-MS. To determine if kratom was present in the different substances, the presence (or absence) of mitragynine was the standard for reaching this conclusion.

Analytic methods used to detect mitragynine, 7-OH, and other alkaloids in kratom include high-performance liquid chromatography (HPLC) (Chittrakarn, Penjamras, and Keawpradub 2012), GC-MS (Oliveira et al. 2016), Chemometrics (Kowalczuk, Łozak, and Zjawiony 2013), HPLC-quadrupole-time-of-flight (QTOF) mass spectrometry (Avula et al. 2015), liquid chromatography-electrospray ionization-mass spectrometry (LC-ESI-MS) (Kikura-Hanajiri et al. 2009), direct analysis in real-time mass spectrometry (DART-MS) (Lesiak et al. 2014), enzyme-linked immunosorbent assay (ELISA) (Limsuwanchote et al. 2014), and capillary electrophoresis–mass spectrometry (CE-MS) (Posch et al. 2012). The analytical method used to analyze the kratom samples in this research was designed to be relevant to forensic drug chemistry laboratories. It was adapted from the Scientific Working Group for the Analysis of Seized Drugs (SWGDRUG) kratom monograph and optimized to detect mitragynine with a minimal analysis time. Mitragynine is specific to *Mitragyna speciosa* and present in the highest concentration of the alkaloids in the plant. Quantitation of mitragynine is complicated due to the presence of the stereoisomers speciogynine and speciocialiatine in *Mitragyna speciosa* (Wang et al. 2014). While 7-OH is 10 times more potent than mitragynine, the concentration of 7-OH detected in the *Mitragyna speciosa* plant is 50–80 times less than that of mitragynine (Lesiak et al. 2014).

Results

Different strains of kratom are grouped by the morphology of the leaves, points at the apex for green (Yak yai), white veins (Tang gua), and red veins (Kan daeng) (Sukrong et al. 2007). Maeng Da is a genetically enhanced variant of Thai kratom, and claimed to be of the most potent form of kratom. While the powders of the various strains can be clearly differentiated in the images shown by different online vendors that sell kratom, the differences are much more subtle in the products as received.

Mitragynine was detected in 13 of the 15 samples: all four liquid samples, the seven powdered kratom samples, and two samples in capsule form (see Table 1). Mitragynine was not detected in the pain relief and natural relaxant pills.

Extraneous peaks were present in all sample extracts (Figure 1). An attempt was made to identify the peaks via comparison to the literature as well as library searches. The three-peak pattern containing mitragynine at 24.944, and peaks at 25.621 and 26.603, appeared in most of the chromatograms of Figure 1. The peak eluting at t(r) = 25.621 was identified as paynantheine or its isomer 3-isopaynantheine (Wang et al. 2014). The last peak in the pattern, t(r) = 26.603 minutes, is tentatively as mitraciliatine, an isomer of mitragynine (Philipp et al. 2009).

Other peaks in the spectrums were determined to be plant sterols such as stigmasterol and campesterol, as well as some fatty acids, by comparison to the NIST05 library. The kratom alkaloid, 7-OH, was not detected in any of the samples due to the low concentration of the drug in kratom and the small sample size used in the analysis.

The two samples in which mitragynine was not detected were both in pill form. These two samples did not list mitragynine or *Mitragyna speciosa* as an ingredient, but were purchased for analysis because they consistently appeared as hits when kratom was used as the search term.

Table 1. Results of laboratory testing.

Sample	Source	Form	Mitragynine
Euphoric Kratom	Online	Powder	Yes
Natural Relaxant	Online	Pill	No
Green Borneo	Online	Powder	Yes
Green Kratom	Online	Capsule	Yes
Maeng Da Thai	Online	Powder	Yes
Pain reliever	Online	Pill	No
Red Borneo	Online	Powder	Yes
Red Vein Herb	Online	Powder	Yes
Feel Good Relief	Online	Liquid	Yes
Pain Relief	Convenience store	Liquid	Yes
Pain Relief	Convenience store	Liquid	Yes
White Borneo 1	Online	Powder	Yes
White Borneo 2	Online	Powder	Yes
Liquid Kratom	Headshop	Liquid	Yes
Gold Kratom	Headshop	Capsule	Yes

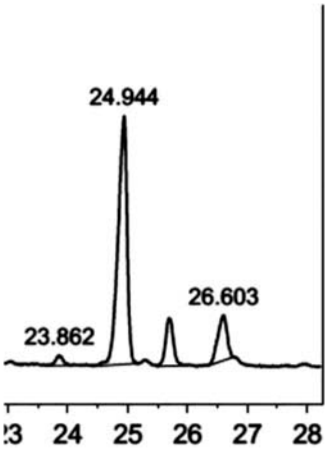

Figure 1. Portion of chromatogram of red vein super herb sample with three kratom peaks.

Discussion

All products containing mitragynine had kratom as part of the product labeling. From our observations, the liquid kratom is primarily marketed for muscle relief, most likely a reference as its use as an opioid replacement. Thus, at least at the time of purchase of these products for study purposes, people were able to purchase products that were actually kratom. While we were unable to detect 7-OH in our samples, that does not necessarily mean that it was absent from the product. Researchers have noted that identifying 7-OH can be difficult since there is a reduced presence of the chemical in kratom (Kikura-Hanajiri et al. 2009; Scott, Yeakel, and Logan 2014). Thus, the absence of 7-OH could be viewed as a limitation of the results. Other substances detected in the samples were consistent with kratom. Undeclared psychoactive adulterants like O-desmethyltramadol were not detected. Keeping this in mind, our results suggest that a user of any of the products purchased for the current study would be unlikely to significantly harm themselves.

Given the presence of both a stimulant chemical and a narcotic chemical in kratom, it is important for future studies to investigate not only how widespread kratom use occurs, but the doses of the substance that users are ingesting. To date, it is unclear how widespread the use of kratom is in many countries. While Ahmad and Aziz (2012) were able to document use patterns in Southeast Asia, as far as we know, such an effort has not been replicated in other areas. Additionally, as Ahmad and Aziz document, prohibition in Southeast Asia has seemed to have little effect on use. It is hard to say whether this is due to widespread acceptance through years of indigenous use (within Southeast Asia) or if it is because kratom is a desirable drug. Furthermore, given the presence of two different chemicals with different chemical properties and a complex dose-response curve in animal testing, there may be divergent safety patterns of different kratom products, depending upon how much mitragynine or 7-OH is included (Yusoff et al. 2016). Determining this would be important in other areas of the world that do not have a long history of kratom use. Kratom has been used for a variety of purposes and could appeal to users seeking either stimulants or narcotic effects. At the same time, kratom has been the subject of several recent news reports, which label it as "addiction in a bottle" (Oder 2015) and note that "It's preying on the weak and the broken" (Schwarz 2016). Considering that these may just be two examples of media reports warning of another supposedly dangerous drug, it is difficult to ascertain the long-term appeal and/or sales of kratom. However, as we found, two products that did not contain mitragynine appeared to be capitalizing on the drug's reputation as a pain killer. Thus, it seems simply advertising a product as kratom may guarantee some sales, regardless of its ingredients.

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